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Spironolactone prescribing in heart failure:

Comparison between general medical patients and those attending a specialist left ventricular dysfunction clinic

R McMullan, B Silke

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SUMMARY

We compared the rate of prescription of low-dose spironolactone among patients with heart failure in a general medical inpatient setting and in a specialist left ventricular (LV) dysfunction clinic. 38% of general medical patients and 72% of patients attending the specialist clinic had been prescribed spironolactone. When contraindications were considered, 54% of patients in the general medical group and 77% of patients in the specialist clinic group were appropriately treated in respect of spironolactone prescribing. Patients attending a specialist LV dysfunction clinic are therefore more likely to be treated with low dose spironolactone, an accepted appropriate treatment for heart failure, than those admitted to general medical and acute geriatric units.Improvement in care for patients with CHF may be achieved either by increasing the use of specialist clinics or by better dissemination of evolving evidence.

INTRODUCTION

In September 1999, the findings of the Randomized Aldactone Evaluation Study[1] (RALES) were published. In this double-blind study, 1663 patients with left ventricular ejection fraction less than 35%, an(NYHA symptom class III-IV were randomised to receive either 25mg spironolactone or placebo. The study was discontinued prematurely after two years because interim analysis showed a 30% reduction in risk of death in the group receiving spironolactone. This is equivalent to a number needed to treat of nine to avoid one death during this two year period[2]. In addition, there was a 35% reduction in risk of hospitalisation for worsening heart failure (equivalent to a number needed to treat of eleven) and significant symptomatic improvement in this group. The low cost of spironolactone implied likely cost-effectiveness.

RALES therefore defined a standard in heart failure management having demonstrated an important contribution from low dose spironolactone in addition to conventional therapies. We appreciate the importance of applying evidence from clinical studies to practice, and it is therefore reasonable to aim to incorporate spironolactone into the medication of all patients with moderate to severe heart failure, except for the few in whom it is contraindicated. We accept that there is no evidence available at present to support its use in mild CHF.

We wished to assess the performance of the specialist left ventricular (LV) dysfunction clinic at the Belfast City Hospital with respect to spironolactone prescribing, comparing this against the prescribing rates for inpatients admitted to the general medical and acute elderly care units.

METHOD

The records of the last 50 patients whose hospital admission was coded with a primary diagnosis of heart failure were analysed prior to 20th February 2000. The 'final' chart related to an admission in December 1999. We also reviewed the records of all 75 patients who were attending the LV dysfunction clinic during the same period. The assumption was made that patients admitted to hospital on the emergency "take-in" due to heart failure and those referred to the specialist clinic

Department of Medicine, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

Dr R McMullan, MB, BCh, Senior House Officer.

Dr B Silke, MD, DSc, FRCPI, Consultant Physician.

Correspondence to Dr McMullan, Kelvin Laboratories, Royal Victoria Hospital.

would be unlikely to have mild CHF, and that almost all could be considered to have moderate-to-severe disease, meriting spironolactone therapy.

Data collected for the purpose of this study were:

1. Whether the patient was receiving spironolactone
2. If not, whether there was any contraindication. We identified three major contraindications, modelling these on those applied in the RALES[1]: serum creatinine >221umol/l, serum potassium >5.0mmol/l and hepatic failure.

RESULTS

Of the 50 general medical inpatients studied, 38% were on spironolactone. Of the remaining patients who were not receiving this drug 26% had at least one contraindication, while 74% were without clear contraindication (Tables I & II and Figure 1). It can therefore be concluded that 46% of these 50 patients were not receiving spironolactone without contraindication.

Of the 75 patients attending the LV dysfunction clinic, 72% were receiving spironolactone. Of those who were not, 19% had at least one contraindication, and 81% had no identifiable contraindication (Tables I & II and Figure 2). Therefore 23% of these 75 patients were not receiving spironolactone despite the absence of clear contraindication.

TABLE I:

Incidence of low dose spironolactone prescribing in heart failure patients in both settings.

	General Medical Inpatients	LV Dysfunction Clinic
Number of patients on spironolactone	19/50(38%)	54/75(72%)
Number of patients not on spironolactone	31/50(62%)	21/75 (28%)

TABLE II:

Proportion of patients with and without contraindication among those not receiving spirono actone in each setting.

	General Medical Inpatients	LV Dysfunction Clinic
Number not on spironolactone with contraindication	8/31 (26%)	4/21 (19%)
Number not on spironolactone without contraindication	23/31 (74%)	17/21 (81%)

DISCUSSION

The comparisons between the two sets of data are interesting but in some ways surprising. Patients who attended the LV dysfunction clinic were more likely to have been prescribed spironolactone; perhaps this is to be expected since physicians running a specialist clinic are probably more likely to be aware of recent evidence within their discipline. However, when the group which was not prescribed spironolactone in each case is examined, it becomes clear that there is little difference in the reason for its omission. One might have expected that the proportion of patients not receiving spironolactone due to contraindication (rather than oversight or lack of familiarity with current evidence) would have been greater among the LV dysfunction clinic patients; this was not the case. The absolute risk of 'oversight', however, was greater among the general medical patient population.

THE ROLE OF ALDOSTERONE ANTAGONISM IN HEART FAILURE

Aldosterone has an established role in the pathophysiology of left ventricular dysfunction. About 30% of patients with chronic heart failure (CHF) have diastolic dysfunction in the setting of normal or near normal systolic function.[3] In such patients, collagen matrix within the myocardium is felt to be the major culprit producing diastolic dysfunction by way of increasing myocardial stiffness. Such fibrotic infiltration also impairs systolic function and contributes to the development of conduction defects and associated arrhythmias.[4]

In addition to collagen, cardiac fibroblasts produce matrix metalloproteinase, an enzyme which

degrades interstitial collagen; these cells are under the influence of the renin-angiotensin-aldosterone system (RAAS).[3] Animal studies have demonstrated increased fibrosis in the setting of hyperaldosteronism and the absence of fibrosis when activation of the RAAS has been prevented. Furthermore, aldosterone stimulates collagen synthesis in cultured cardiac fibroblasts in a dose-dependent manner. In animal studies, in the setting of primary or secondary hyperaldosteronism, spironolactone has been shown to prevent myocardial fibrosis.

High serum aldosterone is a characteristic of CHF, with up to 40% of patients on Angiotensin Converting Enzyme (ACE) Inhibitors having persistently raised levels.[5] In addition to impairing cardiac function by way of causing fibrosis, aldosterone may further increase the arrhythmogenicity of this milieu via inhibition of cardiac noradrenaline reuptake, increased sympathetic activity, decreased parasympathetic tone and impairment of baroreceptor-mediated heart rate variability.[6]

Spironolactone has been found to decrease the amount of a key marker of vascular collagen turnover and also to bring about a decrease in heart rate.[4] Interestingly, this beneficial decrease in heart rate was most prominent in early morning when fatal cardiac events are known to be most common.

Spironolactone has also been shown to improve vascular endothelial dysfunction (characterised by improved responsiveness to vasoactive agents) and also to inhibit the conversion of angiotensin I to angiotensin 11.[7] Perhaps such effects may account at least in part for the mortality benefits of aldosterone antagonism identified in the RALES[1].

It is therefore well established that hyperaldosteronism has an adverse effect on cardiac function, one which may be avoided by the use of aldosterone antagonists. For many years it has been assumed that since ACE inhibitors block aldosterone production spironolactone is unnecessary[8]; however, the finding that it reduced mortality by 30% over a two-year period with concomitant reduction in morbidity must not be ignored. It should be noted that spironolactone is a useful adjunct to, but not substitution for, ACE inhibitor therapy. Indeed there is a feeling that the benefits of spironolactone are likely to be lost if a patient is not concomitantly receiving an ACE inhibitor.

In RALES[1], the major adverse effects of spironolactone in men were gynaecomastia and breast pain, occurring in 10% of the treatment group and in only 1% of the placebo group. Of note, serious hyperkalaemia was minimal in both groups. In support of this, another study found that adding spironolactone to conventional therapy resulted in no significant increase in serum urea, creatinine or potassium.[9] We might, therefore reasonably consider spironolactone to be a safe drug.

CHF is a major public health issue, with general prevalence estimated at 0.4-2.0% in the UK; among the elderly this rises to 10%.[10] It therefore carries significant implications for resource allocation and it is logical that interventions which reduce associated hospitalisations should be considered important.

The cost of a one-year supply of spironolactone is typically £32.85 per patient. Estimation of the total number of patients with CHF in Northern Ireland is fraught with difficulties. Based on extrapolation of Framingham data, the figure could be expected to be between 10000 and 11000. We attempted to corroborate this with an alternative method involving division of the annual number of defined daily doses (DDD) of loop diuretics prescribed by the number of days in the year. This proved unreliable, yielding a figure in excess of 30 000; it failed to exclude patients who would be receiving these agents for reasons other than CHF and it did not account for the many CHF patients who receive doses much greater than the DDD (40mg for frusemide and 1mg for bumetanide).

If we assume that at least 6000 patients in Northern Ireland have moderate-to-severe CHF and are without contraindication to spironolactone therapy, then the cost of treating such a group would be approximately £200000 per annum. Predicting cost-effectiveness is complex and data produced is unlikely to be very reliable, however, a guarded estimate can be made. If one applies the reduction in CHF-associated admissions observed by the RALES investigators (35%) and the estimate that 21.9% of patients with moderate-to-severe CHF require hospitalisation per annum as determined by the SOLVD investigators[11], then of a predicted 1300 admissions per year, around 450 could be avoided. Based on 1997

Belfast City Hospital figures, one such admission costs on average £2436. The potential saving is around £1.1million with an outlay of £200,000; the net saving could therefore be as much as £900,000. Even if these estimates are exaggerated, it seems likely that, with appropriate prescribing, savings on hospitalisation expenditure could negate the cost of any years of life saved.

Spironolactone is the latest addition to several advocated constituents of a CHF treatment regime; however, based on past performance it would seem likely that its widespread incorporation will be a slow process. Reluctance to move practice patterns in phase with new evidence has limited CHF management in the UK. Despite an abundance of evidence favouring outcome benefits and cost-effectiveness achievable by appropriate use of ACE inhibitors, there is a great deal of data to indicate that the 80-90% rates of tolerance estimated in the major mortality studies are poorly reflected in prescribing patterns. Davie and McMurray[12] reported ACE inhibitor prescribing rates of around 66% in hospital and data gathered in 1994 in a community setting in Northern Ireland estimated that perhaps as few as 18% of CHF patients were on such an agent.[10] In a survey of general practitioners' attitudes to CHF management[13], it became apparent that reluctance to prescribe ACE inhibitors was much more strongly related to fear of causing harm than ignorance of proven benefits (of which 98% were aware).

Interesting data are available suggesting that reluctance to prescribe in CHF is variable throughout Europe[14]. The UK typically display a lower rate of prescription, particularly with regard to digoxin and beta-adrenoceptor antagonists. One might expect, therefore, that the rate of prescription of spironolactone will also be lower than average in this country.

Our small study suggests that patients with heart failure who are managed at a specialist LV dysfunction clinic are more likely to receive spironolactone than those who are managed as inpatients in the general medical and acute elderly care units. It also highlights that even in the specialist clinic setting there is room for improvement. Admittedly, the study is not without flaw: there is imbalance in the number of patients in each group and in some cases, clinical decisions (such as to withhold a given treatment) may have been based on observations and measurements not documented. It is not appropriate to presumptively extrapolate these findings to other heart failure treatment interventions, nor to imply actual outcome differences between the two groups; however, our findings support in at least one facet the argument for having teams with a special interest in managing patients with heart failure. This is further supported by data from Chin *et al*[15] identifying an analogous situation relating to ACE inhibitor therapy, whereby general practitioners and general physicians were found to underuse these drugs when compared to cardiologists.

CONCLUSION

Low dose spironolactone has been identified as a safe and rational therapy which decreases mortality, improves symptoms and reduces hospitalisations (thus producing resource utilisation benefits) when added to conventional treatment in patients with moderate-to-severe CHF. When measured against this standard, the finding that we adequately treat only 54% of heart failure patients in a general medical inpatient setting and 77% of patients attending a specialist LV dysfunction clinic provides us with a point from which we might expect to improve; one might alternatively reason that this reflects surprisingly impressive receptiveness to new data over a relatively short time. We have a duty to raise the standard of care for patients with CHF, either by increasing the use of specialist clinics or by improving general physicians' awareness of evolving evidence.

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